The Natural History of Beryllium Sensitization and Chronic Beryllium Disease

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With the advent of *in vitro* immunologic testing, we can now detect exposed individuals who are sensitized to beryllium and those who have chronic beryllium disease (CBD) with lung pathology and impairment. Earlier detection and more accurate diagnostic tools raise new questions about the natural history of sensitization and granulomatous disease. Preliminary data suggest that early detection identifies people who are sensitized to beryllium and that these individuals are at risk for progressing into clinical disease. This article discusses the historical, recent, and ongoing studies germane to our understanding of CBD natural history, including the immunologic and inflammatory basis of the disease, the environmental and host risk factors for disease progression, biological markers of disease severity and activity that may help predict outcome, and the implications for broad-based workplace screening to identify patients at the earliest stages of beryllium sensitization and disease. — Environ Health Perspect 104(Suppl 5):937–943 (1996)

Key words: beryllium, chronic beryllium disease, granuloma, cell-mediated immunity, lymphocyte, natural history, lung disease, pulmonary, immunology, metal toxicity

Introduction

In the past decade we have witnessed a resurgence of interest in beryllium's effects on human health coincident with the realizations that disease due to beryllium continues to occur in industry and that we can use our emerging understanding of the immune system to better detect and diagnose beryllium-related disorders. Chronic beryllium disease (CBD) is a systemic granulomatous disorder that affects the lungs predominantly. New cases continue to be identified despite historical improvements in workplace exposure conditions. Following exposure to beryllium, between 1 and 16% of exposed workers become sensitized to beryllium, as demonstrated using an *in vitro* measure of the beryllium-specific cell-mediated immune response called the beryllium lymphocyte proliferation test (BeLPT), formerly the beryllium lymphocyte transformation test (*1–7*). T lymphocytes recognize beryllium as an antigen triggering cell proliferation, release of inflammatory mediators, and accumulation of inflammatory cells in the target organ. This results in formation of the typical pathologic lesion, the noncaseating granuloma, as well as the accumulation of mononuclear cell infiltrates and fibrosis (Figure 1). CBD can be thought of as a beryllium-specific, cell-mediated immune response gone awry.

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Abbreviations used: CBD, chronic beryllium disease; BeLPT, beryllium lymphocyte proliferation test; CT; computed tomography; PFT, pulmonary function test; DLCO, diffusing capacity for carbon monoxide; BAL, bronchoalveolar lavage; SACE, serum angiotensin converting enzyme activity; A-a gradient, alveolar–arterial oxygen gradient.

Although researchers first speculated on the immune basis of this disorder nearly 50 years ago (*8*), only in the last decade have we been able to capitalize on the immunopathogenesis of CBD in detecting disease at its earliest stages and in redescribing its natural history (*6*). Past notions about the natural history of CBD were constrained by the tools available to clinicians of the 1940s and 1950s. With the advent of immunologic testing for beryllium sensitization (*6,9*), we may now take a fresh look at this disorder starting with some of its earliest biological effects. What emerges is a portrait of CBD that begins with exposure, leads to sensitization, and culminates in the clinically apparent granulomatous and fibrotic disease described by Hardy and colleagues in the 1940s (*10–12*). It is now apparent that the natural history of CBD does not begin with an abnormal chest X-ray or pulmonary function test (PFT), but starts much earlier when the immune system first recognizes beryllium particles as foreign invaders and mounts its stereotypical response to the antigen.

Having learned how to detect sensitization and disease early, new questions arise, to which answers are emerging: *a*) What is the natural history of beryllium sensitization? *b*) Does sensitization lead to clinical CBD? *c*) What is the natural history of subclinical CBD—does it necessarily progress to a clinically apparent illness? *d*) What host or exposure factors influence the natural history of sensitization and of CBD? *e*) Are there biological markers that can help predict the natural history of CBD? and *f*) Will early detection, using the BeLPT as a screening tool, alter the natural history of CBD? Armed with answers to these questions, we will be better able to chart a course toward both primary and secondary prevention of CBD.

This article will review what was known about the natural history of clinical CBD in the era that preceded the use of immunologic markers, review data from recent studies of patients with beryllium sensitization and early disease, and summarize the methodology being used in ongoing longitudinal studies designed to address some of the questions listed above.

Lessons from Past Studies of CBD Natural History

As mentioned, pioneers in the study of CBD accurately described the clinical picture of this disorder in the 1940s and 1950s,

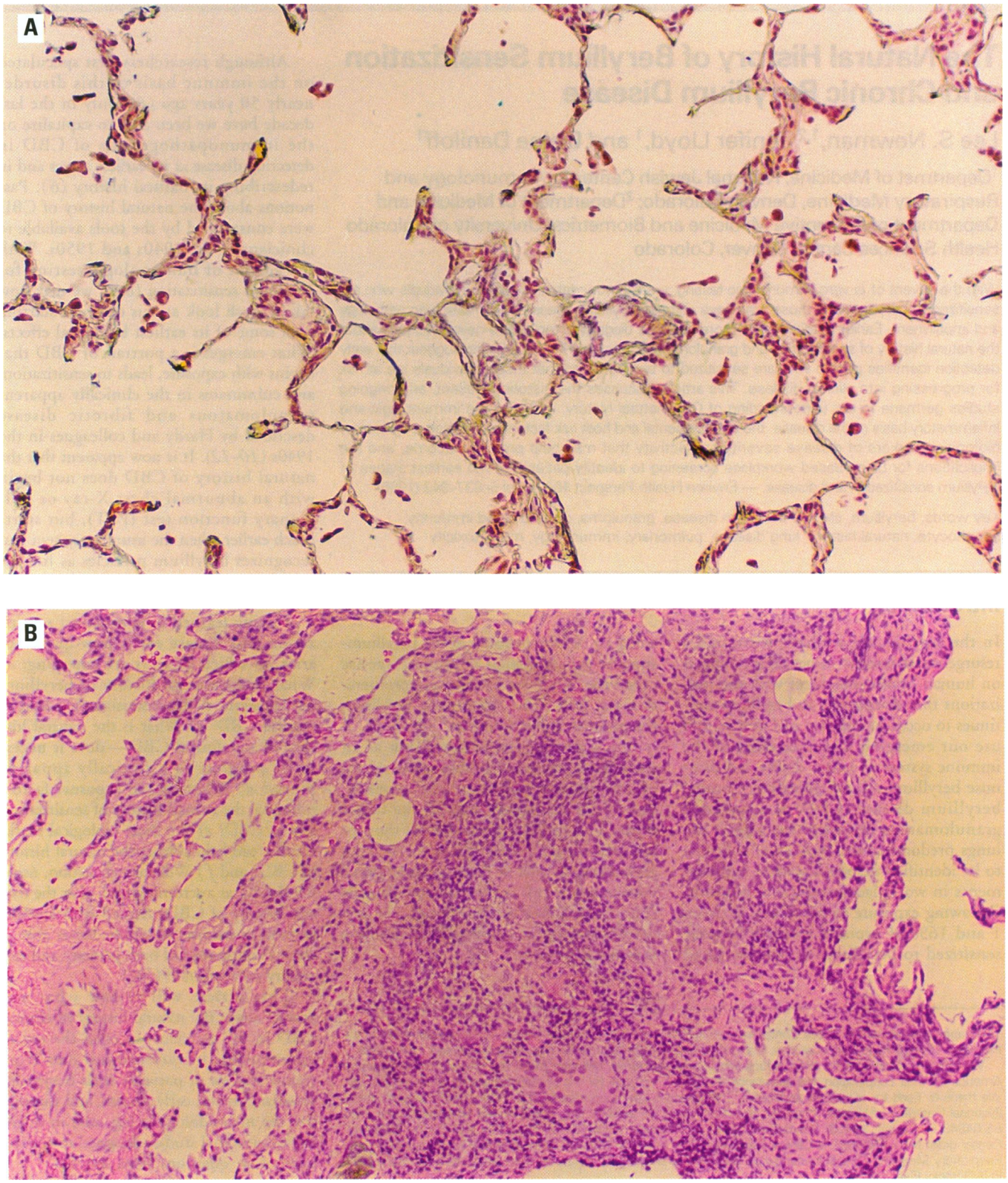

Figure 1. Proposed sequence of pathologic events resulting in chronic beryllium disease. Photomicrograph (*A*), normal lung from a beryllium-sensitized individual (pentachrome stain, 40×); (*B*), early pathologic changes in chronic beryllium disease in which there is a diffuse mononuclear cell interstitial infiltration of the lungs with formation of some multinucleated giant cells, epithelioid cells and lymphocyte aggregates. Hematoxylin and eosin, 10×.

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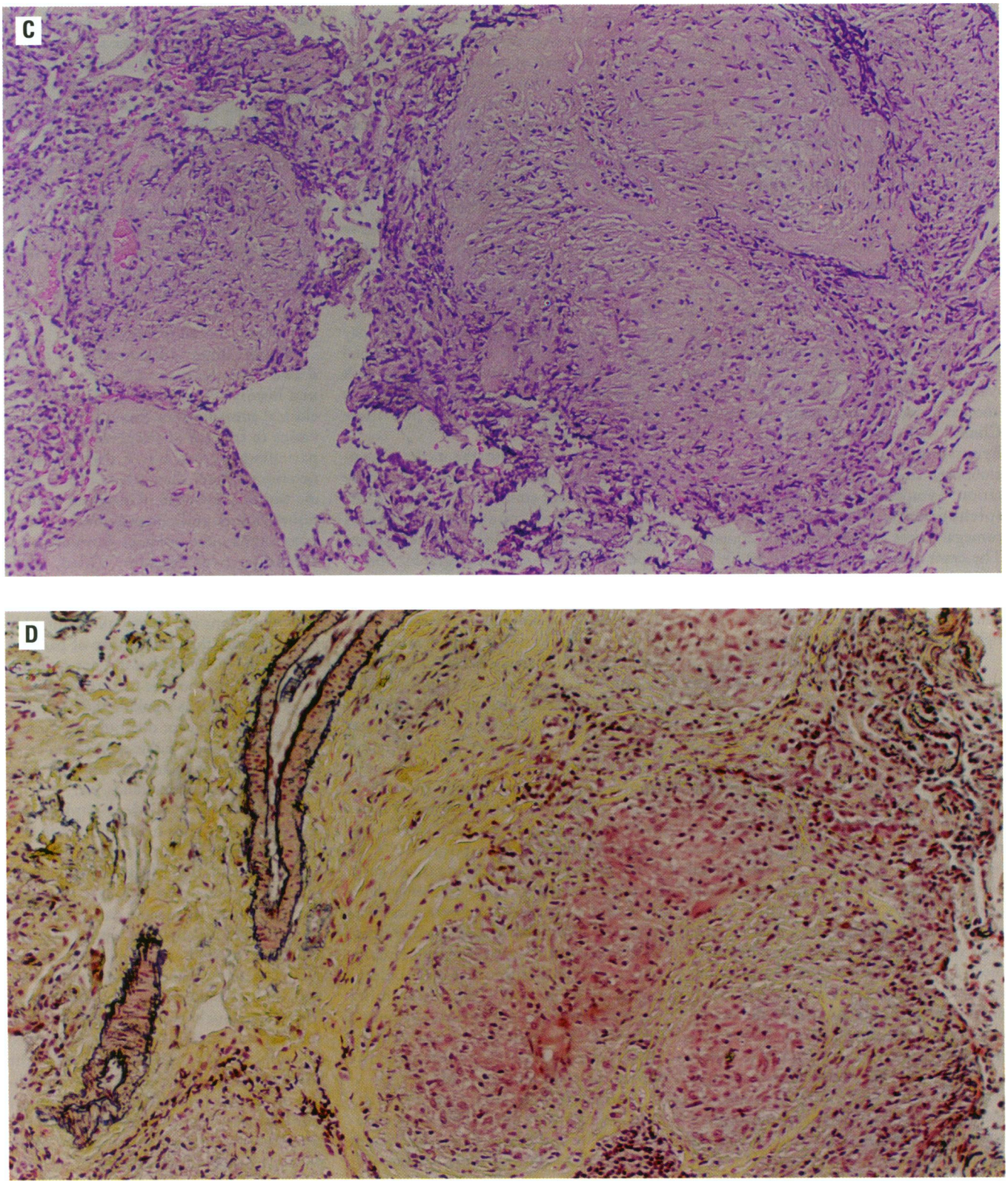

Figure 1 *(continued).* Proposed sequence of pathologic events resulting in chronic beryllium disease (*C*), Later disease showing more typical, well-formed noncaseating granulomas with surrounding areas of mononuclear cell interstitial infiltration and varying degrees of fibrosis. Hematoxylin and eosin, 10×. (*D*), Pentachrome stain of noncaseating granulomas demonstrates the dense circumferential accumulation of collagen (yellow) surrounding the granulomas. Pentachrome, 40×.

using medical history, physical examination, chest radiograph, and pulmonary function testing. More sophisticated tests such as computed tomography (CT) scanning, immunologic tests like the beryllium lymphocyte proliferation test (BeLPT), and measures of the pulmonary inflammatory response such as bronchoalveolar lavage (BAL) enhance our ability to identify and study early disease. However, these earlier works offer a valuable depiction of the natural history beginning with the first clinically obvious signs of CBD (*10–12*).

At the Sixth Saranac Symposium, in 1947, Hardy reported her first observations of CBD natural history (*11*). Patients presented typically with a combination of respiratory and systemic symptoms, most commonly including weight loss, dyspnea, anorexia, cough, chest pain, and fatigue. Clinical signs frequently included cyanosis, hypertrophic osteoarthropathy (digital clubbing), and dry bilateral rales on auscultation. Lymphadenopathy, hepatomegaly, splenomegaly, skin lesions, and thyromegaly were found, but less frequently. The cases characterized in the 1940s and 1950s were severe and detected at a late stage, as reflected by the frequency with which patients "presented" with evidence of right-sided heart failure and cor pulmonale.

Typically, the clinical cases of CBD at that time presented first with weight loss and shortness of breath, later followed by PFT changes and by abnormalities in the chest radiograph (*10,11*). When pulmonary physiologic alterations developed, patients were found to have different patterns. Some had normal lung volumes and airflow but abnormal gas exchange as reflected by the diffusing capacity for carbon monoxide (DL_{CO}) (*13*) or by arterial blood gas analysis at rest and with exercise (*14,15*). Others developed air flow limitation first, followed later by a restriction in lung volumes. Others who presented with more advanced disease showed a predominantly restrictive pattern. When chest radiographs became abnormal, the parenchymal pattern ranged from diffuse fine nodular opacities to larger nodules. These nodules eventually consolidated into larger masses associated with local pleural and subpleural thickening. Hilar and mediastinal adenopathy was common but not uniformly present. Notably, patients presented often with symptoms and PFT abnormalities in advance of any radiographically apparent abnormalities, suggesting that the chest radiograph was a relatively insensitive marker of disease severity. Alternatively, some patients had abnormal chest radiographs but were asymptomatic, or symptomatic without abnormalities on routine spirometry. The conclusion drawn by Hardy in 1955 was that the natural history of CBD varies among affected individuals (*12*). Although data were not shown, that article suggested that some patients with abnormal chest radiographs could remain free of "disability." Unfortunately, no information exists concerning the degree to which more sensitive tests of pulmonary physiologic derangement such as exercise physiology with measurement of arterial oxygenation were employed. Furthermore, it was suggested that some individuals may "recover" from CBD either "with residual evidence of irreversible pathology" or with "no evidence of disease." Again, there is a lack of primary data showing how these conclusions were drawn.

Taken in composite, the medical literature suggests that once CBD is clinically apparent, it will continue to progress if left untreated. Does spontaneous remission occur? In 1978, Sprince and colleagues reported that the chest radiographic abnormalities disappeared in 9 of 18 untreated patients within 3 years of reduced exposure. Gas exchange abnormalities improved in 13 of 20 who had arterial hypoxemia (*16*). Unfortunately these cases had only limited assessments. Only four had biopsy confirmation of disease and no cases received immunologic assessment to lend greater specificity to the diagnoses. In a brief report by Nishikawa in 1980, CBD was confirmed in eight cases by lung biopsy and blood BeLPT. Two of the eight cases showed radiographic clearing within one year of removal from exposure (*17*). In 1969, Stoeckle described a case of complete remission of CBD but only after treatment with adrenocorticotrophic hormone (ACTH) (*18*). Taken together, these studies suggest that under some circumstances, patients with CBD may undergo remission or at least clinically stabilize upon removal from exposure, although most studies indicate that disease progression is the general rule even after the patient leaves the workplace (*19,20*).

Published mortality rates for CBD range from 5.8 to 38%. This wide variation is influenced in part by the duration of clinical follow-up, but there is some evidence that characteristics or type of exposure may affect mortality as well. In 1958, Peyton and colleagues reported on the mortality in 561 occupational cases of beryllium disease, including 240 acute cases (for whom the mortality rate was 7%) and 348 CBD cases. In the CBD group as a whole, 28% died. The mortality rate was 18% among beryllium extraction workers, 28% among fluorescent lamp workers, and 38% among those working with beryllium alloys, beryllia ceramics, or in research and development. Unfortunately, the authors did not indicate the number of years that elapsed between diagnosis and death (*19*). The reason for the apparent differences in the mortality rates by industry remains an enigma. We do not yet know if the early detection of CBD will lead to earlier therapeutic intervention with corticosteroids and a lower mortality rate (below).

Several important conclusions can be drawn from the past studies of CBD natural history. First, the disease varies in its clinical presentation. Second, the disease varies in its rate of progression. Not all patients progress, but if they do, some deteriorate faster than others. While some die within a few years of diagnosis in respiratory failure and cor pulmonale, others experience a more insidious downhill course extending over decades. Third, while removal from exposure may be medically prudent, it is not known to what extent such restrictions will change the natural history for more than a minority of patients. Fourth, the earlier studies did not systematically examine the risk factors for disease progression, such as smoking status; gender; race; genetic makeup; duration, magnitude, or type of exposure; industry in which exposure occurred; or mixed exposures to other metals, solvents, cutting fluids, etc.

Based on past clinical studies and anecdotes, it is reasonable to hypothesize that a number of factors may affect the natural history of CBD. These may include the industry in which the exposure occurred, the magnitude, frequency, and duration of the exposure, principles of particle size and solubility, as well as possible host factors such as genetic makeup, smoking habits, and, as suggested by Hardy, intercurrent life stresses such as pregnancy/lactation, combat, and surgery. More data are needed to examine such questions. What is the relevance of the past studies of natural history to our understanding of CBD today? The industry has changed. Fluorescent lamps no longer contain beryllium phosphors, although a large number of the cases upon which the past studies of natural history are based were fluorescent lamp workers (*21*). Today, cases originate increasingly in secondary use industries such as machining of the metal and its alloys, dental alloy

preparation, and ceramics. Although disease still occurs, the mean level of exposure has been lower in the 1980s and 1990s than in previous decades, at least for most beryllium users. Some of the cases of CBD initially presented with acute beryllium pneumonitis (*21*) that progressed into the chronic disease, whereas acute disease is now distinctly rare. Earlier studies relied upon a case definition that was prone to potential misclassification, leading to the possibility that some cases follow a different course because they have a different etiology. In addition, the natural history studies were usually conducted as a series of cross-sectional analyses of the U.S. Beryllium Disease Case Registry, not as a true longitudinal study tracking natural history within individuals. With the availability of immunologic tests, in the 1980s it became possible to define CBD with much greater specificity. Furthermore, by using the blood BeLPT, the disease that is studied today is identified at a much earlier stage than has been described prior to the late 1980s.

We conclude that if we are to understand the natural history of CBD as we will know it in decades to come, it will be necessary to take a fresh approach that *a*) relies upon the best available case definition, one that lends the greatest specificity without unnecessarily excluding cases; *b*) focuses on cases that are identified as only being sensitized to beryllium without evidence of disease; *c*) employs the most sensitive physiologic, radiographic, and laboratory tests available to track disease progression; *d*) has a longitudinal, not cross-sectional, design; and *e*) concomitantly tracks demographic variables and covariants such as smoking and exposure that may influence natural history.

Recent Studies Pertaining to CBD Natural History

Several important clinical and epidemiologic investigations have helped set the stage for the conduct of studies that meet the needs described above. In the mid-1980s, our group worked to improve the blood BeLPT such that it could be used to screen large numbers of exposed workers for evidence of beryllium sensitization (*22*). Reasons for using the BeLPT and a discussion of its merits and limits are presented elsewhere in this supplement (*23*). We have conducted studies of 3 groups to date: a pilot study of nuclear weapons workers, a subsequent study of 895 of these workers, and population-based studies in two beryllia ceramics plants. Through this series of investigations, Kreiss, Newman, and coworkers demonstrated that it was possible to identify individuals who are sensitized but who do not have disease, to identify individuals with subclinical illness, and to correct missed diagnoses in more advanced cases of disease (*2,3,6,22*). In one of these population-based studies, we examined the positive and negative predictive value of the various clinical tests that physicians use to screen for beryllium disease in industry (*3*). The only test with high positive and negative predictive value was the blood BeLPT. As expected based on the earlier case series, the chest radiograph was relatively insensitive. Spirometry, symptom reporting, and clinical examination had even lower positive predictive values. We concluded that to identify and track the natural history of beryllium sensitization and disease, it is necessary to develop more sensitive clinical and biological indicators of disease activity and progression. This led to a series of studies of the merits of other clinical testing modalities for detecting the clinical consequences of sensitization and early disease.

Toward the goal of developing more sensitive markers of severity and progression, Pappas and Newman reexamined the utility of pulmonary function testing, DL_{CO}, and exercise testing with indwelling arterial line in both the early and the advanced stages of CBD (*24*). They observed that 57% of CBD patients identified through workplace screening with the BeLPT have measurable physiologic abnormalities at the time of diagnosis, supporting the value of early detection as a means of finding clinically relevant disease. The most common physiologic derangements in early CBD were found in the measures of gas exchange: rising dead space to tidal volume ratio during exercise and abnormal fall of the PaO_2 and rise in the alveolar-arterial oxygen gradient (A-a) during exercise. By comparison, spirometry, body plethysmographic lung volumes, and DL_{CO} proved insensitive (*24*). These observations were consistent with the physiologic changes seen in CBD in the 1940s by Wright and colleagues (*14,15*). While exercise testing is relatively time consuming, expensive, and invasive, the information obtained is far superior to that achieved using the conventional tools of pulmonary medicine (*24*). Such testing is needed to determine if a patient with early disease has physiologic impairment or if the disease is progressing. Preliminary results from our longitudinal study discussed below suggest that measures of gas exchange and exercise limitation provide a more sensitive means of tracking changes in CBD over time.

Conventional chest radiography is insensitive in detecting CBD. We recently examined whether thin-section CT would improve our ability to recognize CBD noninvasively (*25*). Chest radiography was compared with thin-section CT in a group of 15 CBD patients who had abnormal chest radiographs and a second group of 13 patients who had normal chest radiographs as read by certified B-reader using the International Labor Organization (ILO) Classification. In the group with normal chest X-rays, CT detected one or more of the following abnormalities in three-quarters of the patients: nodules, septal lines, areas of ground-glass attenuation, and bronchial wall thickening. The clinically advanced cases showed more nodules and septal lines (a result of fibrosis) than the early, X-ray-normal cases. We conclude that thin-section CT is relatively more sensitive than plain radiography. CT may be helpful in gauging the severity of early disease and warrants further study as a means of monitoring disease progression. The CT still misses up to one-quarter of biopsy-proven cases of CBD identified through workplace screening with the BeLPT. Thus, a negative scan should not be used to decide against biopsying patients with abnormal BeLPTs.

In sarcoidosis, a granulomatous disease of unknown etiology, serum angiotensin converting enzyme (SACE) activity is frequently elevated and has been associated with the body burden of granulomas. Similarly, SACE is elevated in patients with CBD. But in one study that included patients with early disease, only 22% had abnormally elevated SACE levels (*26*). The SACE activity, however, correlated with the severity of pulmonary physiologic and radiographic abnormalities in CBD, suggesting that it may prove useful as a biological marker of disease progression or of response to therapy. This warrants further study in the longitudinal examination of natural history in CBD. Similarly, it may be possible to use other blood indicators of the magnitude of the inflammatory response or the degree of lymphocyte activation as nonspecific biomarkers of disease severity and disease progression. Promising candidates include measures of key proinflammatory cytokines known to be present in increased amounts in the lungs of patients with CBD, including tumor necrosis factor-α, and interleukin-6 (*27*).

CBD is characterized by the development of large numbers of lymphocytes within the lungs. This can be measured by bronchoalveolar lavage (BAL), which is a process of instilling fluid into a portion of lung through a bronchoscope, withdrawing the fluid, and counting the numbers and types of cells recovered (*6,28,29*). The BAL cellularity and lymphocytosis reflects the degree of pulmonary inflammation. Inflammation results in injury and in physiologic impairment. It stands to reason that if we measure directly the magnitude of the inflammatory response in the lungs of patients with sensitization or with CBD, we might predict the effects of inflammation on lung physiology and physical impairment. In a recent study of a large number of patients with CBD, we began to address this question by comparing the BAL findings at the time of diagnosis with other clinical parameters such as pulmonary function testing, DL_{CO}, chest radiograph profusion of small opacities, and measures of exercise tolerance and gas exchange during exercise (*28*). The data suggest that the higher the number of white blood cells and lymphocytes in the BAL, the more severe the exercise limitation, A-a gradient, PaO_2, and DL_{CO} abnormalities in CBD. Future studies will examine whether these baseline BAL measures predict change in pulmonary physiologic impairment over time.

Longitudinal Study of the Natural History of Beryllium Sensitization and CBD

As a result of the population-based studies by Kreiss and colleagues, we can now initiate a longitudinal study of beryllium sensitization and early CBD. This study, being conducted at National Jewish Center for Immunology and Respiratory Medicine, has three goals: to determine the natural history of sensitization and disease, to determine the best predictors of disease progression, and to determine the host and environmental factors that may modify the risk of disease progression. We hypothesize that sensitization leads to clinical CBD; that CBD progression varies among individuals, i.e., that the natural history is nonuniform; and that it is possible to identify individuals at greatest risk for disease progression using biological markers of the inflammatory and immune response. Figure 2 outlines schematically the likely sequence of events in CBD and the potential outcomes that we would expect to observe longitudinally.

Since 1986, this longitudinal, observational study has enrolled all new cases of beryllium sensitization or of biopsy-proven CBD in a research protocol that measures annually: (1) symptoms, occupational and environmental exposures, and personal risk factors, (2) physical findings, (3) spirometry and body plethysmographic lung volumes, (4) DL_{CO}, (5) exercise capacity on a cycle ergometer with indwelling arterial line for blood gas analysis, (6) chest radiograph profusion of small opacities, (7) SACE, (8) blood BeLPT, (9) BAL variables including the cell count, differential, T cell subsets, BeLPT, as well as analyses of other cell-associated markers of inflammation and cell activation, and (10) transbronchial biopsy in the sensitized group. Baseline evaluation also includes thin-section CT scanning.

To date, this study has enrolled a total of 99 patients, 72 of whom have clinical CBD, 50 with disease detected through workplace screening, and 22 with sensitization alone. The mean age is 52 years (range 32–80 years). Reflecting the general workforce at the industrial plants screened, the demographic distribution is predominantly Caucasian and male. The groups are equally divided among ever- and never-smokers with the exception that there are more ever- and current-smokers in the sensitized, nondisease group. Subjects are divided equally between those exposed in the ceramics industry and those exposed in the manufacture of nuclear weapons or through other metal machining-related operations.

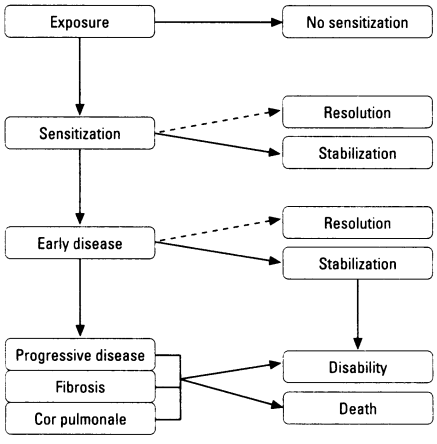

Figure 2. Proposed schema of the events and outcomes for individuals exposed to beryllium. Solid lines indicate known outcomes. Broken lines indicate hypothetical outcomes. Note that some individuals with early disease may stabilize but be left with some degree of impairment and disability. Corticosteroids may have an effect on progressive disease, but their role in early disease management is not known.

While half the clinical CBD cases are on corticosteroids at the time of enrollment, fewer than 10% of the CBD subjects who enter through workplace screening programs are on treatment with either oral or inhaled forms when they enroll.

Preliminary Conclusions

The mean duration of follow-up of these cohorts as of October 1994 has been 2.8 years for the clinical CBD group, 2.8 years for the screening-identified CBD group, and 2.3 years for the sensitized only group. Thus, it is too early to draw many conclusions from this study of a slowly progressive, chronic disorder. Nonetheless, several preliminary, qualitative conclusions can be made at this time based on the longitudinal data and based on the population-based studies discussed above.

First, sensitization can occur in the absence of CBD (*2*). We follow 22 patients who clearly had repeatedly abnormal blood BeLPTs but who had no symptoms, no physical abnormalities, and normal spirometry, PFTs, DL_{CO}, exercise capacity, gas exchange, chest radiographs, bronchoalveolar lavage, and even normal lung biopsies at the time of entry in the study.

Second, sensitization can progress into clinical CBD (*9*). Although the duration of follow-up has been relatively short to determine the rate at which this occurs, of the six individuals sensitized who have been followed for more than 5 years, three have developed CBD based on the emergence of abnormal clinical findings, symptoms, physiology, and increasingly lymphocytic lavage and noncaseating granulomas on lung biopsy. Not all patients with sensitization have developed CBD, but a longer period of follow-up will be needed to determine the frequency with which progression to CBD occurs.

Third, after exposure to beryllium, for those patients who develop CBD, the biological alterations occur in the following sequence: development of beryllium-specific immunity; gradual emergence of a chronic inflammatory response within the target organ, e.g., lung; pathological alterations in the target organ; measurable physiologic derangement; disability; and in some cases, death.

Fourth, we conclude that it is feasible to conduct a longitudinal study of the natural history of sensitization and CBD, but that due to the rate of disease progression and the variability between individuals, a long period of study and a large number of study subjects will be required.

Given the absence of good data concerning the natural history and the variables that may affect outcome, such studies are needed. We hope that early intervention will prevent long-term disability and death for the many sensitized and diseased patients identified through workplace screening and surveillance efforts.

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